Heterologous Production of Polyketides in Fungi

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Heterologous Production of Polyketides in Fungi

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Polyketides are the source of some of the most potent antibiotics and anticancer agents available today. They constitute a large group of natural compounds, produced primarily by fungi and bacteria. However, the productivity is often very low in the native producer. Thus, expression of polyketide gene clusters in an industrially relevant microorganism presents a great potential. Towards fulfilling this potential we are working with the three fungal species, *viz. S. cerevisiae*, *A. niger* and *A. nidulans,* which are all well suited as hosts for polyketide production. The overall goal of the project is to construct microbial super hosts through the use of state of the art genetic engineering and *in silico* modeling tools.

Polyketides belong to one of nature's most diversified groups of compounds. Among the polyketides can be named the cholesterol lowering agent lovastatin and the antibiotic erythromycin. We are studying two polyketides: mycophenolic acid (MPA) which is used as an immunosuppressant and 6-methylsalisylic acid (6-MSA) that has antibiotic properties. By studying three different species capable of producing heterologously expressed polyketides, we aim at designing more efficient polyketide cell factories that will work in a plug-and-play fashion. The overall strategy towards achieving this goal is illustrated in figure 1.

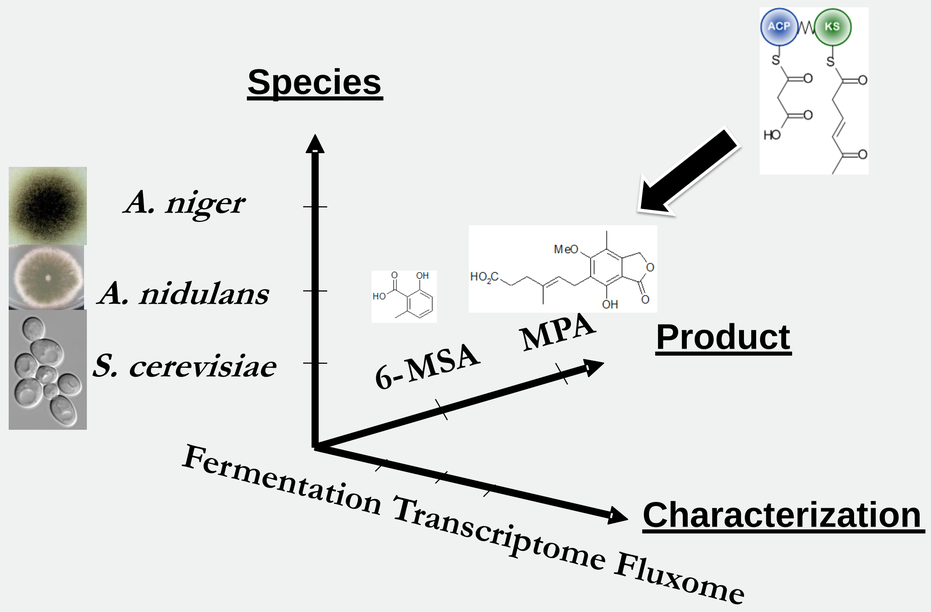
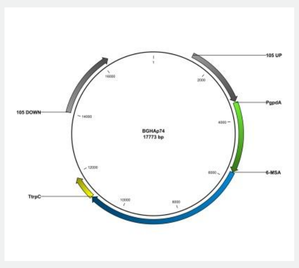


Fig. 1 Overall strategy for the construction of polyketide cell factories.

Targeted Integration of the 6-MSA PKS in *A. nidulans*



Gene Targeting

A. nidulans

Plug Extraction

HPLC

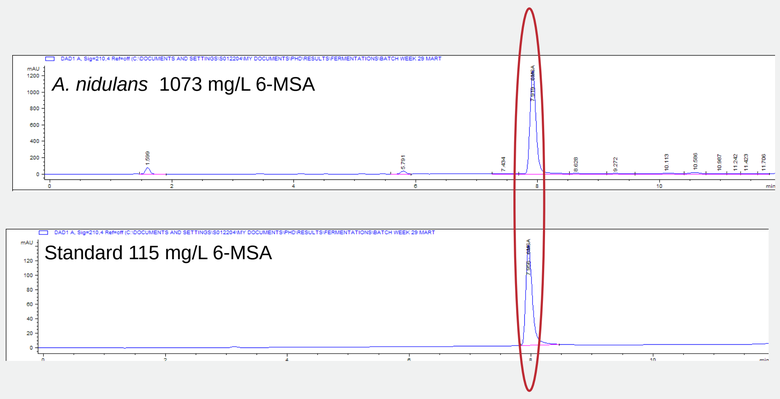
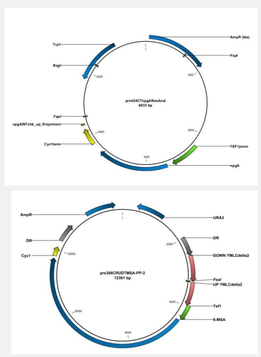
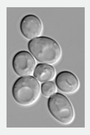


Fig. 2 6-MSA production in *A. nidulans* after targeted integration of the 6-MSA synthase.

Targeted Integration of the 6-MSA PKS and *npgA* PPTase in *S. cerevisiae*

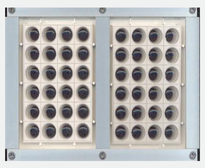


Gene Targeting



S. cerevisiae

Microtiter Plates



HPLC

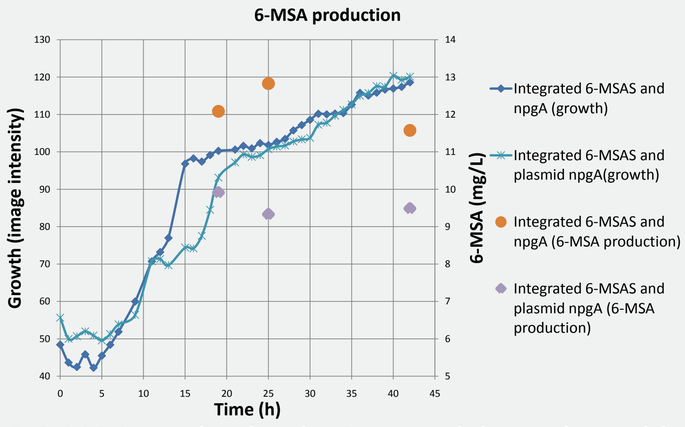


Fig. 3 6-MSA production in *S. cerevisiae* using a high throughput microtiter platform after targeted integration of the *6-MSAS* and the *npgA* PPTase. The strain was compared with a strain that only has the *6-MSAS* integrated and the PPTase on a multicopy plasmid. As having only one copy of the PPTase did not decrease 6-MSA production, it is clear that the polyketide synthase expression is the limiting factor in polyketide production.

The stable heterologous production of polyketides in *S. cerevisiae* and *A. nidulans* presents the first step in the construction of efficient cell factories. Polyketide synthases are proving to be the source of several new medically relevant compounds. Having a polyketide cell factory platform will therefore be a significant step towards economic and sustainable production of this important class of natural products.

Wattanachaisaereekul *et al.*, PhD. Thesis. Technical University of Denmark 2007,

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